

Remarks

Claims 1 to 14 are pending in the instant application. Claim 2 is amended and new claim 15 is added herein. Entry of the amendments to the claims is appropriate because the amendments directly address issues raised by the Examiner and simplify the issues in the event of an appeal. Accordingly, Applicants respectfully request entry of the amendments and reconsideration of the claims in light of the remarks below.

No new matter is added by way of the amendments to the claims. Applicants amend the claims solely to enhance clarity. Specifically, claim 2 is amended and claim 15 is added to include a numerical definition of prevalence. Support for a numerical indication of prevalence can be found, for example, on page 4, lines 10-19, of the instant specification.

Claim Rejections Under 35 U.S.C. § 112

Claims 2 and 8 to 10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Office action alleges that the “specification does not provide a clear, specific, limiting definition” of the term prevalent. Applicants amend claim 2 to recite that “the bleb preparation that is not deficient in PorA is derived from a meningococcal strain with a serosubtype that is selected from among the most prevalent, the second most prevalent, the third most prevalent, and the fourth most prevalent serosubtypes in a country of use.” In view of this amendment to claim 2, Applicants believe that the rejection of claims 2 and 8-10 under 35 U.S.C. § 112 is rendered moot, and the rejection should be withdrawn.

Preliminary Remarks

Claims 1-9 of the instant application are directed to a “multivalent meningococcal bleb composition comprising a bleb preparation deficient in PorA in that it has less than 80% of the amount of PorA as compared to the same quantity of blebs made from strain H44/76 and a bleb preparation that is not deficient in PorA compared to blebs made from strain H44/76.” It is a feature of the claimed subject matter that the multivalent meningococcal bleb compositions include at least one bleb preparation that is deficient in PorA in combination with at least one bleb preparation that is not deficient in PorA. The mere provision of multivalent meningococcal bleb compositions is NOT the subject matter of claims 1-9. Rather, it is the recognition of the inventors that combinations of blebs that include at least a

first bleb preparation deficient in PorA and at least a second bleb preparation that is not deficient in PorA provide superior immune responses to heterologous strains, and offer benefits in production over vaccines made with the many different blebs that would be necessary to provide adequate protection against strains of the various heterologous serosubtypes. As stated in the instant specification (paragraph bridging pages 3-4), the claimed multivalent meningococcal bleb compositions provide “a good compromise by minimizing the number of blebs in a vaccine, whilst still providing good specific and general protection against prevalent strains and against mutation of these stains or the introduction of new serogroup B strains when cases from prevalent strains are reduced.” In view of the foregoing, Applicants respectfully request reconsideration of the claims.

Claims Rejections Under 35 U.S.C. § 102 and 103

Claims 1-9 are novel and non-obvious in view of Berthet *et al.*

Claims 1 to 9 remain rejected under 35 USC 102 (b) as being anticipated by Berthet, *et al.* (WO 01/09350). Applicants traverse the rejection, and respectfully request reconsideration of the claims in view of the following remarks.

Under U.S. patent law “[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987). Thus, in order for Berthet *et al.*, to anticipate claims 1-9 of the instant application, Berthet must expressly or inherently disclose a multivalent meningococcal bleb composition that includes at least one bleb preparation that is deficient in PorA in combination with at least one bleb preparation that is not deficient in PorA.

The Examiner contends that “Berthet *et al.* disclose a multivalent vaccine comprising mixtures of meningococcus bleb preparations...” To support this contention, the Examiner points to page 36, lines 15-19 of WO 01/09350, which states in pertinent part: “it is envisaged that the formulation could alternatively contain wild-type meningococcus B bleb preparations from 2 or more (preferably several) strains belonging to several subtype/serotypes (for instance chosen from P1.15, P1.7,16, P1.4, and P1.2).” Applicants do not disagree that Berthet teaches a multivalent bleb preparation. However, this passage does not teach that the different bleb preparations are selected such that at least one of the bleb preparations is deficient in PorA and that at least one other bleb preparation is not deficient in PorA. The

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Examiner contends that “Berthet *et al.* specifically discloses a mixture of strains H44/76 and CU-385 (see page 35, lines 20-26). Because CU385 is deficient in PorA and H44/76 is not deficient in PorA, the mixture disclosed by Berthet *et al.*, meets all of the limitations of the instant claims.” This simply is not the case.

Contrary to the Examiner’s assertion, page 35, lines 20-26 of WO 01/09350, does not relate to compositions containing mixtures of blebs. Rather page 35, lines 20-26 relate to bleb preparations that are immunoprotective against a set of heterologous strains to be selected from the major clonal groups known. This passage further stipulates that the bleb preparation should result in seroconversion that produces bactericidal activity against meningococcus B strains that should have a different PorA type from the bleb production strain...most preferably all 5 of strains H44/76, M97/252078, BZ10, NGP165 and CU385. Thus, WO 01/09350 teaches that a single bleb preparation can be produced that is immunoprotective against multiple strains (including both strains H44/76 and CU-385) of meningococcus B, and not that the bleb preparations should be derived from CU-385. All mention of strain CU-385 is made with reference to this strain being used in bactericidal assays to measure killing activity, and never in the context of the vaccine production strain.

The passages of page 35 and 36 discussed above simply do not suggest either expressly or inherently that the multivalent bleb preparation contain at least one bleb preparation that is deficient in PorA in combination with at least one bleb preparation that is not deficient in PorA. As a preliminary matter, nothing in either of these passages expressly states that any of the proposed strains is or should be deficient in PorA. Furthermore, because as the Examiner admits (in the Office Action of November 28, 2006, page 4, lines 5-7) not all strains of the serotype P1.15 (or any of the other serotypes suggested on page 36, lines 11-14) are deficient in PorA, WO 01/09350 does not inherently disclose multivalent bleb preparations that include at least one bleb preparation that is deficient in PorA in combination with at least one bleb preparation that is not deficient in PorA. A claim limitation is inherently disclosed by a reference if the limitation is “the natural result flowing from the explicit disclosure of the prior art.” *Schering Corporation v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003). That is, the result must “necessarily and inevitably” result from the disclosure of the prior art. *Schering Corporation v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1378 (Fed. Cir. 2003). Because each of the disclosed serotypes/serosubtypes includes numerous strains that are not deficient in PorA, the

suggestion in WO 01/09350 to make mixtures of blebs from strains of different serotypes/serosubtypes does not provide multivalent bleb preparations that necessarily and/or inevitably contain at least one bleb preparation that is deficient in PorA in combination with at least one bleb preparation that is not deficient in PorA. Therefore, WO 01/09350 cannot reasonably be interpreted even as inherently disclosing the subject matter of claims 1-9. In conclusion, Berthet *et al.*, neither expressly nor inherently anticipates the subject matter of claims 1-9, and the rejection should be withdrawn.

Additionally, claims 1-10 remain rejected under 35 U.S.C. § 103(a) over Berthet *et al.* (cited above) in combination with Lehmann (APMIS 99:769-772 1999). Applicants traverse. The Examiner's position is flawed in at least the following respects.

- 1) As discussed above, WO 01/09350 simply does not teach multivalent bleb compositions that contain at least one bleb preparation that is deficient in PorA in combination with at least one bleb preparation that is not deficient in PorA. More specifically, as indicated above, the contention that page 35, lines 11-14 discloses compositions including combinations of blebs of strains H44/76 and CU-385 is simply incorrect.
- 2) WO 01/09350 does not teach any vaccine compositions containing the strain CU-385. Rather as discussed above, this reference teaches the desirability of vaccine compositions that are immunoprotective against strain CU-385.
- 3) Furthermore, the Examiner relies on the Applicant's own specification for the teaching that strain CU-385 is deficient in PorA. While Applicants do not dispute that "any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning," the use of "knowledge gleaned only from applicant's disclosure" is expressly prohibited. *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). The Examiner has pointed to nothing other than the instant specification that would inform one of skill in the art that CU-385 is deficient in PorA. This is precisely the sort of use of the Applicants' disclosure that constitutes improper hindsight reasoning.
- 4) Lehmann does not remedy any of the above failings. On the contrary, Lehmann merely teaches vaccines containing outer membrane vesicles of strain H44/76 (e.g., in combination with capsular polysaccharides and/or adjuvants.

Berthet *et al.* in combination with Lehmann simply do not teach all of the elements of claims 1-10. Moreover, there is nothing in either of these references, in the absence of the Applicants' own specification, that would teach or motivate one of skill in the art to select a strain (such as CU-385) that is deficient in PorA to produce a multivalent meningococcal bleb composition. In addition, nothing of record, absent the Applicants' own specification, provides any expectation that a multivalent bleb composition containing at least one bleb preparation that is deficient in PorA in combination with at least one bleb preparation that is not deficient in PorA would successfully provide the benefits articulated in the instant specification.

Claims 1-9 are novel and non obvious with respect to Granoff *et al.*

Claims 1 to 9 also remain rejected under 35 USC §102(b) as anticipated by or, in the alternative, under U.S.C. §103(a) as obvious over Granoff, *et al.* (WO 02/09643). Applicants traverse.

The Office action states on page 5, lines 27-29, that: "Granoff *et al.* disclose vaccines that contain blebs from multiple strains of *Neisseria*. Granoff *et al.* disclose the "Norwegian Vaccine" which contains blebs from strain H44/76 (see page 5, lines 5-10), and Granoff *et al.* disclose mixtures which contain blebs from strain CU-385 (see page 48, lines 22-23). Both of these statements are factually incorrect.

On page 5, lines 5-10, Granoff states: "Antisera from control animals given two sequential immunizations of a outer membrane vesicle vaccine prepared at the National Institute of Public Health, Oslos Norway, from a single *Neisseria meningitidis* serogroup B strain, H44/76 (B:15:P1.7,16; "Norwegian vaccine"), reacted by flow cytometry and were bactericidal against only serogroup B strains that were of the same serosubtype (i.e. P1.7,16) or strains having an epitope similar to the P1.16 epitope (such as P1.10-4 strains). Thus, Granoff is in fact referring to a vesicle preparation from a single *Neisseria meningitidis* serogroup B strain, H44/76, and not to a vaccine that contains blebs from multiple strains of *Neisseria*.

On page 48, lines 22-23, Granoff states: "Immunization with the mixture of antigens elicited broader bactericidal activity than expected but the titers measured against the some strains tended to be much lower than those obtained in animals given the sequential CHORI

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vaccine immunization (e.g. strains CU385 and 1000, titers of 1:128 and 1:128 after CHORI vaccine aluminium phosphate vs. titers of <1:4 and 1:6 in antisera prepared against three injections of the mixed antigen/aluminium phosphate.” Page 44 of the Granoff specification clearly indicates that the antigens in the CHORI sequential immunization “vaccine,” and, therefore, in the mixtures, are RM1090, BZ198 and Z1092. The passage on page 48 is further placed in context by reviewing Figure 8. Bactericidal activity against 15 different strains, including CU-385, was measured in serum obtained from mice that had been injected with either 1) a first injection of a strain RM1090 antigen, followed by a second injection of a strain BZ198 antigen, followed by a third injection of a strain Z1092 antigen (the “CHORI vaccine”); or 2) injections of a mixture of antigens of strains RM1090, BZ198 and Z1092. Serum from the injected mice was collected and evaluated in a complement-mediated bactericidal activity assay in which killing of various strains, of which CU-385 is one strain, was quantitated. The results of the assay (tabulated in Figure 8) showed that the CHORI vaccine, and to a far lesser extent, the mixture of RM1090, BZ198 and Z1092 antigens, elicited an immune response against heterologous strains. Thus, the passage on page 48 simply does not disclose any combinations or mixtures that include CU-385 (or for that matter any other strain that is recognized as being deficient in PorA). Again, reference to CU-385 is only made with respect to its use in an experimental model to test bactericidal activity of sera generated against other strains of meningococcus.

The Office Action also alleges that Granoff *et al.* further disclose individual bleb vaccines that each comprise strains with the serosubtypes P1.15 (CU-385) and P1.7,16 (see figure 1). However, Figure 1 does not in fact disclose strain CU-385. Figure 1 merely discloses a strain of serosubtype P1.15. As discussed above, there are many strains in addition to CU-385 that fall into the serosubtype P1.15.

In addition, the Examiner admits that Granoff *et al.*, does not explicitly disclose that the bleb vaccine mixture should contain strains with serosubtypes P1.15 (CU-385) and P1.7,16. This raises two important points. First, Granoff *et al.*, do not disclose any compositions containing mixtures that include blebs of serosubtype P1.15, much less compositions including strain CU-385. More importantly, it must be recognized that the mere combination of blebs of different strains (including mixtures of serosubtypes P1.15 and P1.7,16) is NOT the subject matter of claims 1-9. Rather it is a combination of blebs that includes at least one bleb preparation that is deficient in PorA in combination with at least

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one bleb preparation that is not deficient in PorA. This is true regardless of the specific serosubtypes selected. Strain CU-385 is simply one favorable example of a strain that is deficient in PorA (that happens to be of serosubtype P1.15) that can be used in combination with any of a variety of strains of different serosubtypes, e.g., that are selected to correspond to one or more strains that are currently prevalent in an intended country of use. Thus, even the use of serosubtypes P1.15 and P1.7,16 does not anticipate or render obvious claims 1-9, unless it can be shown that the particular strains used include a strain that is deficient in PorA in combination with a strain that is not deficient in PorA. Granoff does not provide this teaching. In conclusion, nothing in Granoff, as written, modified, or in combination with any other art of record, anticipates or renders obvious claims 1-9. Accordingly, the rejection should be withdrawn.

Conclusion

On the basis of the amendments and remarks above, Applicants believe that the claims are now in condition for allowance. In the event that any substantive issues remain, Applicants respectfully request an Advisory Action at an early date. If the Examiner believes that a telephonic interview would expedite prosecution and/or clarify or simplify any of the issues under consideration, the Examiner is invited to contact the undersigned to arrange for an Examiner's interview, or to discuss the status of this application.

Respectfully submitted,



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